Safety and Pharmacokinetics of Hyperimmune Anti-Human Immunodeficiency Virus (HIV) Immunoglobulin Administered to HIV-Infected Pregnant Women and Their Newborns

Pharmacokinetic Study Group*

The pharmacokinetics and safety of hyperimmune anti-human immunodeficiency virus (HIV) intravenous immunoglobulin (HIVIG) were evaluated in the first 28 maternal-infant pairs enrolled in a randomized, intravenous immunoglobulin (IVIG)—controlled trial of HIVIG maternal-infant HIV transmission prophylaxis. Using 200 mg/kg, mean half-life and volume of distribution (Vd) in women were 15 days and 72 mL/kg, respectively, after one and 32 days and 154 mL/kg after three monthly infusions, with stable 4 mL/kg/day clearance. Transplacental passage occurred. Newborn single-dose half-life, Vd, and clearance were 30 days, 143 mL/kg, and 4 mL/kg/day, respectively. HIVIG rapidly cleared maternal serum immune complex–dissociated p24 antigen, and plasma HIV-1 RNA levels were stable. Mild to moderate adverse clinical effects occurred in 2 of 103 maternal and 2 of 25 infant infusions. No adverse hematologic, blood chemistry, or immunologic effects were seen. HIVIG is well-tolerated in HIV-infected pregnant women and their newborns, clears antigenemia, crosses the placenta, and exhibits pharmacokinetics similar to those of other immunoglobulin preparations.

Congenital or perinatal HIV infection is acquired by transmission from mother to fetus or infant during gestation or parturition. Several lines of evidence suggest that factors protective against maternal-infant transmission include higher levels or specific types (or both) of endogenous maternal antibodies directed against human immunodeficiency virus (HIV). Although not replicated universally [1–3], a number of studies have indicated lower transmission rates from infected pregnant women with high antibody titer or with high-affinity/avidity antibody to conserved portions of HIV-1 glycoprotein 41 [4], to the CD4 binding site [5] or the V3 loop of glycoprotein 120 [6–9], or to p24 gag protein [10].

All of the foregoing studies, however, were of antibodies directed against laboratory-adapted strains of HIV-1 rather than clinical isolates and did not evaluate functional activity. Ultimately, in vivo activity against wild strains of virus may be more relevant. In this regard, maternal neutralizing antibody may be an important determinant of protection. Several investigators have reported that nontransmitting mothers more frequently have such antibody to their own virus than do transmitting mothers and that transmitting mothers rarely have neutralizing antibody against their child’s own isolate [11–13]. It has been reported furthermore that mothers with autologous neutralizing antibody frequently have antibodies that also neutralize heterologous primary isolates [11].

By analogy with the success of prophylactic and therapeutic regimens using passive immunization with specific hyperimmune globulin products derived from human plasma against other bloodborne viral pathogens, such as hepatitis B virus or cytomegalovirus, the development and evaluation of hyperimmune anti-HIV immunoglobulin preparations for prevention or
treatment of HIV infection and disease have received attention. Several studies in symptomatic HIV-infected adults treated with HIV hyperimmune globulin or plasma preparations [14–18] and in one child with AIDS who received passive immunotherapy with HIV immune plasma [19] have shown disappearance of p24 antigenemia and inhibition of plasma viremia.

However, as with many drugs and biologics, the extent of evaluation of these investigational products in pregnant women or newborns ranges from limited to none. We report the results of an evaluation of the safety and pharmacokinetics of hyperimmune anti-HIV intravenous immunoglobulin (HIVIG) in HIV-infected pregnant women and their newborns conducted in the first 28 subjects enrolled in AIDS Clinical Trials Group (ACTG) protocol 076 treatment regimen [21].

Materials and Methods

Study design. Pharmacokinetic sampling was performed in the first 28 maternal-infant pairs enrolled in a multicenter, double-blind, randomized, controlled trial of the efficacy of HIVIG for the prevention of maternal-infant HIV transmission in HIV-infected pregnant women and newborns receiving zidovudine. Eligible subjects were HIV-infected pregnant women between 20 and 30 weeks of gestation whose CD4+ T lymphocyte absolute counts were ≤500/μL and who required zidovudine treatment for medical indications other than pregnancy.

Women received study treatment with HIVIG or with standard intravenous immunoglobulin (IVIG) in a dose of 200 mg/kg of body weight by intravenous infusion every 28 days until delivery. Maternal infusions were administered starting at a rate of 0.02 mL/kg/min for 30 min, then gradually increased as tolerated to a maximum of 0.08 mL/kg/min. Infants received a single infusion of HIVIG or IVIG according to the maternal treatment assignment in a dose of 200 mg/kg of body weight within 12 h after birth. Infant infusions were begun at a rate of 0.01 mL/kg/min and doubled at 15-min intervals as tolerated, to a maximum rate of 0.08 mL/kg/min.

Management of infusion-related adverse experiences was specified by the study protocol, which allowed for alteration of infusion rate and for antipyretic and antihistamine premedication. Clinical and laboratory evaluations were performed at baseline, each infusion visit, and 26 weeks postpartum in women and at birth and 1, 2, and 6 weeks of age in infants. All women and infants received concomitant zidovudine treatment according to the ACTG protocol 076 treatment regimen [21]. Informed consent was obtained for all women and infant subjects participating according to local institutional review board and federal guidelines [22] and regulations [23].

Product description. HIVIG (manufactured as HIV-IG by NABI, Boca Raton, FL) is a preparation of highly purified human immune globulin containing high titers of antibody to HIV structural proteins. It contains considerable functional activity in virus neutralization and antibody-dependent cytotoxicity assays [24]. This intravenous IgG solution is prepared from plasma of multiple HIV-seropositive donors from geographically diverse regions of the United States who are selected according to strict clinical and biological criteria. Donors are clinically asymptomatic, maintain CD4+ T lymphocyte counts ≥400/μL, and are negative for HIV-1 p24 antigen, nonreactive for hepatitis B surface antigen, and nonreactive for antibody to hepatitis C virus. The donor plasma contains high titers of anti-p24 antibody (a potential indicator of strong immune response to HIV).

The manufacture of HIV-IG includes multiple steps to inactivate or partition (or both) HIV, including solvent/detergent treatment of the plasma and fractionation by Cohn-Onley alcohol precipitation. The inactivation procedures used in the manufacturing process reduce infectious virus concentrations in starting material by a factor of ≥9 log10 (unpublished data: Validation study for removal and inactivation of viruses by North American Biologicals, Inc.'s immune globulin process. Quality Biotech Protocol C31279.00, 6 November 1995).

The final product is a 5% (50 mg/mL) solution that contains 98% monomeric IgG. It contains anti-p24 antibody titers of >1:20,000 by Abbott (Abbott Park, IL) HIVAB p24 (rDNA) EIA, is negative for HIV-1 p24 antigen and negative for HIV-1 RNA by polymerase chain reaction (PCR), is unable to infect phytohemagglutinin-stimulated normal human lymphocytes in the presence of interleukin-2, and is negative for hepatitis C virus RNA by PCR. Against HIV-1 Env and other laboratory-adapted strains, the product demonstrates high virus neutralizing activity, high antibody binding to related V3 loop peptides, and inhibition of syncytium formation [20]. HIVIG also has been shown to neutralize primary patient isolates, including several from infected neonates [25–27].

Standard IVIG (Gammimune N; 5% globulin intravenous [human]; Bayer, West Haven, CT) was used in patients randomized to the control arm of the study. The experimental (HIVIG) and control (IVIG) study immunoglobulin preparations were visually indistinguishable from one another. Treatment assignment was known only to the study’s data coordinating center and to the pharmacists who prepared and dispensed the study immunoglobulin preparations. Three different lots of HIVIG were used over the course of the study. For any given maternal subject, material from a single lot was used for all infusions, and all but 4 infants received material from the same lot that their mother received.

Specimen collection and processing. Peripheral blood was collected by venipuncture. In women, 4 mL of whole blood was collected in a serum separator tube immediately before infusion and at 1 h, 24 h, 7 days, 14 days, and 28 days after infusion (immediately before the next infusion) for each infusion cycle, and at 28 days postpartum. For the first infusion cycle, an additional specimen was collected at 3 days after infusion. An additional 2.6 mL of maternal whole blood was collected in acid-citrate-dextrose anticoagulant at the preinfusion and 24-h, 14-day, and 28-day postinfusion time points for quantitative virologic assays requiring plasma. From infants, 4
mL of whole blood was collected in a serum separator tube from the placental cord at delivery and by peripheral venipuncture before infusion and at 1 h, 24 h, 7 days, 14 days, and 28 days after infusion. The selection of these sampling times was guided by an optimal sampling strategy with a D-optimality criterion [28].

Serum was separated from fresh whole blood by centrifugation, aliquoted into sterile polypropylene tubes, held at 4°C, and shipped overnight using cold packs on the day of collection or next business day to a central repository. Each specimen was aliquoted on receipt into 4 sterile polypropylene freezer vials for specified assays and stored at −70°C.

Plasma was separated from fresh whole blood within 6 h of collection. Whole blood was held at 4°C and centrifuged at 800 g relative centrifugal force for 20 min at 23°C. Plasma was removed, recentrifuged as before, aliquoted into sterile polypropylene freezer vials, stored at −70°C, and shipped overnight on dry ice monthly to a central repository.

All assays (except quantitative HIV-1 RNA plasma levels) were run prospectively in a single central laboratory with approved performance in the National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS, virology quality assurance program [29]. Specimens were subjected to only a single freeze-thaw cycle and were identified to the laboratory only by code, without indication of patient treatment assignment.

Pharmacokinetic assays. A pharmacokinetic assay panel that included HIV-1 p24 antibody titer was performed on serum collected from each maternal or infant subject at each serum collection time point.

HIV-1 p24 antibody titer was measured by Abbott HIVAB p24 (rDNA) EIA over eight 6-fold serial dilutions (1:6 to 1:1,679,616) and calculated as the mean value of triplicate replicates for each specimen. All specimens from a given infusion cycle for a given patient were assayed within the same run to reduce variability, and with a new standard curve generated for each run. For analysis of individual patient data, a significant change in HIV-1 RNA plasma level (increase or decrease) was defined a priori as ≥0.7 log_{10} (5-fold) change in RNA copy number from entry or from the last preinfusion draw that was sustained on two or more sequential determinations >24 h apart.

Statistical analysis. Geometric mean values for p24 antibody serum titer, ICD serum p24 antigen, and quantitative plasma HIV-1 RNA determinations were calculated as the antilog of the arithmetic mean of the logarithms of the measured values. Corresponding SD limits above and below the geometric mean were calculated as the antilog of the sum of the arithmetic mean and SD of the logarithms of the measured values, and the antilog of the difference of the arithmetic mean and SD of the logarithms of the measured values, respectively. Because the data distributions for these measures demonstrated some degree of positive skewness, the geometric mean was used to stabilize the variance and more closely approximate the median value than the arithmetic mean. Analysis of variance was used for comparison of means, using two-sided P values with α = .05 in all cases.

HIV-1 p24 antibody concentration data were analyzed by fitting a series of one- and two-compartment pharmacokinetic models to the concentration-time data using weighted least-squares regression [28]. The models were formulated to accommodate repetitive, nonuniform intravenous infusions of HIVIG. Concentration data were weighted by the inverse of an estimate of the variance for the HIV-1 p24 antibody assay, where a value of 20% was used for the assay coefficient of variation. Selection of the model that best described the antibody concentration data was accomplished by calculation of the Akaike information criterion [31]. The pharmacokinetic parameters assessed included the volume of distribution (Vd), terminal elimination half-life (t1/2), area under the curve (AUC), and total body clearance (CL). Separate analyses were performed for the p24 antibody concentration data pertaining to each HIVIG infusion that a pregnant woman received. For the newborn, the pharmacokinetics of HIV-1 p24 antibody were determined by an analysis of the cord specimen (birth) titer and all postinfusion values following the single dose of HIVIG.

Results

In total, 28 maternal-infant subject pairs were included in the pharmacokinetic analysis. Demographic and clinical char-
Characteristics of women at study entry are outlined in table 1. Treatment groups were similar with respect to age distribution, racial and ethnic origin, gestational age, CD4⁺ T lymphocyte count, zidovudine treatment history, and presence of ICD p24 antigenemia. Twelve women received HIVIG; 16 received IVIG. Two infants died shortly after birth and were not evaluated (1 HIVIG-assigned subject with perinatal asphyxia and severe hypoxic ischemia and 1 IVIG-assigned subject with extreme prematurity). Distribution of gestational age at birth was similar in HIVIG-treated (median, 39 weeks; mean ± SD, 38.9 ± 2.0; range, 34–41) and IVIG-treated infants (median, 39.0 weeks; mean ± SD, 39.4 ± 1.7; range, 36–42). Preterm (<37 completed weeks of gestation) delivery occurred in 2 infants in each group.

Data from 1 HIVIG-treated woman who demonstrated an extremely high baseline serum p24 antibody titer (134,636) were excluded from calculations of geometric mean p24 antibody titers and antigen levels. No cord specimen was drawn from 1 HIVIG-treated infant. Specimens for HIV RNA quantitation were unavailable from 1 woman in each treatment group.

Infusions in the pregnant women were well tolerated. Only 2 (1.9%) of 103 HIVIG or IVIG infusions were associated with adverse experiences, which consisted of one episode of vomiting and one episode of headache, both of moderate severity. No adverse experience required permanent discontinuation of study immunoglobulin infusions. There were no significant differences between treatment groups in mean values of hematologic (absolute neutrophil count, hemoglobin, mean corpuscular volume, red blood cell count, or white blood cell count) and lymphocyte immunophenotype measures (CD3⁺, CD3⁺CD4⁺, CD3⁺CD8⁺, and CD19⁺ relative and absolute cell counts) through 26 weeks postpartum.

Infusions in newborns were well tolerated. Of 25 HIVIG or IVIG infusions, adverse experiences were seen in 2 and consisted of one episode of mild flushing and one episode of moderately severe vomiting. No adverse experience prevented completion of study immunoglobulin infusion. There were no significant differences between treatment groups in mean values of hematologic, blood chemistry (electrolytes, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and total and direct bilirubin), or lymphocyte immunophenotype measures through 6 weeks of age with the exceptions that platelet counts were lower (141,000 vs. 392,000/µL), absolute CD3⁺ and CD3⁺CD4⁺ cell counts were higher (5570 vs. 4183 and 3740 vs. 2745/µL, respectively), and absolute and relative CD3⁺CD8⁺ cell counts were higher (1654 vs. 995/µL and 23% vs. 18%, respectively) at 6 weeks in HIVIG-treated infant subjects. These differences were not considered clinically meaningful.

Results of pharmacokinetic parameter analyses are shown for HIVIG-treated women and newborns in table 2. The pharmacokinetic data best fit a two-compartment model. In women, the mean HIVIG total body clearance remained stable at 4 mL/kg/day, but distribution volume and terminal half-life increased with more infusions. The mean $V_d$ and $t_{1/2}$ for the first infusion ($n = 11$) were 72 mL/kg and 15 days, respectively, compared with 154 mL/kg and 32 days for the third infusion ($n = 9$).

Figure 1 shows the geometric mean p24 antibody serum titer and serum ICD p24 antigen concentration-time curves in women by infusion and by treatment group. Trough (28 days postinfusion) p24 antibody concentrations appeared to rise with successive HIVIG infusions (from 1902 to 2574 to 3403), and sustained elevation of p24 antibody was observed at 28 days postpartum in HIVIG-treated compared with IVIG-treated women (1403 vs. 53).

Rapid, sustained suppression of serum ICD p24 antigen from baseline (102 pg/mL) was observed in HIVIG-treated women, and no increase in either serum ICD p24 antigen or quantitative levels of hematologic, blood chemistry (electrolytes, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and total and direct bilirubin), or lymphocyte immunophenotype measures through 6 weeks of age with the exceptions that platelet counts were lower (141,000 vs. 392,000/µL), absolute CD3⁺ and CD3⁺CD4⁺ cell counts were higher (5570 vs. 4183 and 3740 vs. 2745/µL, respectively), and absolute and relative CD3⁺CD8⁺ cell counts were higher (1654 vs. 995/µL and 23% vs. 18%, respectively) at 6 weeks in HIVIG-treated infant subjects. These differences were not considered clinically meaningful.

## Table 1. Characteristics of ACTG protocol 185 pharmacokinetic study participants at entry.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIVIG (n = 12)</th>
<th>IVIG (n = 16)</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–24</td>
<td>4 (33)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>25–29</td>
<td>2 (17)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>30–39</td>
<td>6 (50)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1 (8)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (17)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (75)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>Gestational age at randomization, weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–27</td>
<td>5 (42)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>≥28</td>
<td>7 (58)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Pre-entry CD4⁺ T lymphocyte count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200/µL</td>
<td>4 (33)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>≥200/µL</td>
<td>8 (67)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Prerandomization zidovudine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Begun &gt;180 days earlier</td>
<td>3 (25)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Begun ≤180 days earlier</td>
<td>9 (75)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>HIV ICD p24 antigenemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>7 (58)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Absent</td>
<td>5 (42)</td>
<td>8 (50)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%); percentages may not total 100 due to rounding. ACTG = AIDS Clinical Trials Group; HIVIG = hyperimmune anti-HIV intravenous immunoglobulin; IVIG = intravenous immunoglobulin; ICD = immune complex–dissociated.
HIV-1 RNA plasma level was seen at trough p24 antibody concentration (28 days after infusion). In the 7 of 12 HIVIG-treated women who had detectable serum ICD p24 antigen at entry, antigen became nondetectable following day 1 after infusion and remained nondetectable throughout treatment, with the sole exception of a single borderline reactive result (32 pg/mL) in 1 patient during the second infusion cycle. This effect of suppression of detectable antigen with HIVIG persisted at 28 days postpartum, with serum p24 antigen detectable in only 3 women (42 pg/mL).

In the 8 of 16 IVIG-treated women who had detectable serum ICD p24 antigen at entry, no such decrease was seen. Serum p24 antigen level remained near or above baseline (122 pg/mL) on all determinations except for the final draw of the third infusion cycle, when an apparent transient decline was observed. However, this data point may be subject to sample size-induced instability of the mean (4 positive results from specimens available in only 7 of 13 potentially evaluable subjects). Levels of antigen were increased on next evaluation at 28 days postpartum (181 pg/mL).

Figure 2 shows for each treatment group the geometric mean concentration-time curve from day 0 to day 28; RTU = reciprocal titer units; CL = total body clearance. No significant increase or decrease in HIV-1 RNA plasma level was seen at trough p24 antibody concentration (28 days after infusion). In the 7 of 12 HIVIG-treated women who had detectable serum ICD p24 antigen at entry, antigen became nondetectable following day 1 after infusion and remained nondetectable throughout treatment, with the sole exception of a single borderline reactive result (32 pg/mL) in 1 patient during the second infusion cycle. This effect of suppression of detectable antigen with HIVIG persisted at 28 days postpartum, with serum p24 antigen detectable in only 3 women (42 pg/mL).

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Table 2. Serum p24 antibody pharmacokinetic parameters of HIVIG treatment in HIV-infected pregnant women and their newborns.

<table>
<thead>
<tr>
<th>Group, HIVIG infusion (n)</th>
<th>t1/2, days</th>
<th>Vd, mL/kg</th>
<th>AUC0-28, RTU × day</th>
<th>CL, mL/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (11)*</td>
<td>15.4 (60%)</td>
<td>72 (18%)</td>
<td>204,943 (88%)</td>
<td>4.1 (46%)</td>
</tr>
<tr>
<td>2nd (11)*</td>
<td>15.4 (42%)</td>
<td>73 (39%)</td>
<td>370,617 (147%)</td>
<td>3.7 (54%)</td>
</tr>
<tr>
<td>3rd (9)*</td>
<td>31.6 (101%)</td>
<td>154 (83%)</td>
<td>210,462 (66%)</td>
<td>4.3 (45%)</td>
</tr>
<tr>
<td>Newborns</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (11)</td>
<td>30.0 (48%)</td>
<td>143 (32%)</td>
<td>204,287 (86%)</td>
<td>4.1 (53%)</td>
</tr>
</tbody>
</table>

NOTE. Data are mean (coefficient of variation). HIVIG = hyperimmune anti-HIV intravenous immunoglobulin; t1/2 = terminal elimination half-life; Vd = volume of distribution; AUC = area under p24 antibody concentration-time curve from day 0 to day 28; RTU = reciprocal titer units; CL = total body clearance.

* Excludes 1 patient with extremely high baseline p24 antibody titer.

IVIG-treated subjects. There were no significant differences between or within treatment groups.

Figure 3 shows the geometric mean p24 antibody serum titer concentration-time curve in HIVIG-treated newborns compared with IVIG-treated newborns.

Among the HIVIG-treated maternal-infant pairs, the newborn cord geometric mean serum p24 antibody titer was 4906, with a range of 1162 to 46,407. The mean ratio of cord blood to extrapolated maternal serum p24 antibody titer at delivery was 1.16 (coefficient of variation, 55%). There was some suggestion that higher serum p24 antibody titer in newborns at birth was related to the time since last maternal dose and to greater gestational age of the newborn and that increased p24 antibody clearance in newborns was related to greater gestational age at birth (data not shown). In contrast, the geometric mean cord serum titer of p24 antibody in newborns of IVIG-treated women was only 54.

HIVIG pharmacokinetics in newborns were best described by a two-compartment model. Following a single infusion, mean terminal elimination half-life in HIVIG-treated infants was 30 days, mean volume of distribution was 143 mL/kg, and mean total body clearance was 4.1 mL/kg/day. Substantially increased serum p24 antibody levels (≥3557) persisted for at least 28 days in HIVIG-treated compared with IVIG-treated infants.

Discussion

The phase I safety and pharmacokinetic study conducted within ACTG protocol 185 revealed that infusion of HIVIG or IVIG was well-tolerated when administered to pregnant women and newborns. A low incidence of immediate infusion-related adverse experiences was seen in mother and infant, and these events did not require permanent discontinuation of study immunoglobulin infusions.

HIVIG pharmacokinetics in HIV-infected pregnant women were best described with a two-compartment model. Typical...
Figure 1. Serum p24 antibody titer (left panels) and immune complex-dissociated (ICD) p24 antigen levels (right panels) with time for infusion cycles 1, 2, and 3 (top to bottom) in hyperimmune anti-human immunodeficiency virus intravenous immunoglobulin (HIVIG)- and standard intravenous immunoglobulin (IVIG)-treated HIV-infected pregnant women. Data are geometric mean ± SD. n, range of nos. of patient samples assayed for each treatment group; n+, range of nos. of samples that were positive for ICD p24 antigen.
Elevated p24 antibody titers at birth in newborns of HIVIG-treated compared with IVIG-treated women, and increased ratios of newborn to maternal p24 antibody titer, indicate that substantial transplacental passage of HIVIG occurred. This confirms previous work that maternal infusions of specific antibody can result in the birth of newborns with high titers of these antibodies [35].

Administration of HIVIG produced substantial elevation in serum titers of p24 antibody in women and newborns. Rising trough concentrations of p24 antibody were produced with repeated HIVIG dosing in women. In contrast with HIVIG-treated subjects, p24 antibody serum levels in IVIG-treated women and newborns remained low following infusion.

Viral markers of HIV activity were measured in this study to evaluate the safety of the products and confirmed that no increase in circulating maternal levels of HIV serum ICD p24 antigen or plasma HIV-1 RNA occurred following infusion of either HIVIG or IVIG. In women receiving HIVIG, no rebound increase above baseline in either serum ICD p24 antigen or HIV-1 RNA plasma levels was observed at trough p24 antibody levels (28 days after infusion), indicating that no short-term enhancement of viral replication occurred with HIVIG.

In women who had measurable serum ICD p24 antigen at study entry, antigen became and remained nondetectable throughout all infusions in virtually all HIVIG-treated subjects but remained positive in subjects treated with IVIG. Moreover, use of the immune complex dissociation technique implies that this disappearance of detectable antigen represents clearance of circulating viral antigen and not merely antigen-antibody immune complex formation. There was no consistent change in HIV-1 RNA plasma level within or across infusion cycles in women receiving either HIVIG or IVIG.

values for HIVIG disposition during the first two infusions were a $t_{1/2}$ of ~15 days, $V_d$ of ~70 mL/kg, and clearance of 4 mL/kg/day, consistent with other immunoglobulin preparations. $V_d$ and $t_{1/2}$ were observed to increase after three infusions. The change in $V_d$ may be related to increasing gestational age and transfer of immune globulin to the fetus. Since $t_{1/2}$ is a function both of $V_d$ and of clearance (which remained stable), $t_{1/2}$ was observed also to increase. Interpatient variability in pharmacokinetic parameters in pregnant women was greater than that seen in a phase I study of HIVIG in HIV-infected men with advanced disease [32] but was consistent with interpatient variability observed with use of other immunoglobulin products in pregnancy [33].

HIVIG disposition in the newborn demonstrated biexponential decay, with a mean $t_{1/2}$ of 30 days and clearance of 4 mL/kg/day. These pharmacokinetic parameter values are consistent with those of other immunoglobulin products in neonates [34].

Figure 2. Serum p24 antibody (Ab) titer and immune complex–dissociated (ICD) p24 antigen (Ag) levels at entry and at postpartum day 28 (top) and HIV-1 RNA plasma level with time on study (bottom) in hyperimmune anti–human immunodeficiency virus intravenous immunoglobulin (HIVIG)–treated and standard intravenous immunoglobulin (IVIG)–treated HIV-infected pregnant women. Data are geometric mean ± SD. $n$, nos. of patient samples assayed for each treatment group; $n+$, nos. of samples that were positive for ICD p24 antigen.

Figure 3. Serum p24 antibody (Ab) titers with time in hyperimmune anti–human immunodeficiency virus intravenous immunoglobulin (HIVIG)–treated compared with standard intravenous immunoglobulin (IVIG)–treated newborns. $n$, range of nos. of patient samples assayed for each treatment group.
This study confirms the short-term safety of HIVIG, as demonstrated by a low rate of infusion-related complications, no observed adverse effects on hematologic, blood chemistry, or immunologic measures, and no evidence of enhanced viral replication. However, the present analysis did not measure the long-term safety of this treatment. Such evaluation will be provided as part of the large phase III study (ACTG protocol 185), in which the efficacy of HIVIG for prevention of maternal-fetal transmission of HIV-1 will be tested and in which follow-up of the pharmacokinetic study subjects continues. The effect of repeated HIVIG administration to HIV-infected pregnant women and to newborns at birth, with discontinuation of maternal treatment following delivery, on maternal disease status (beneficial, detrimental, or neither), and the impact of treatment on ability to assess infant infection status, will be evaluated by follow-up through 18 months postpartum in women and infants enrolled in ACTG protocol 185, with close monitoring of clinical, immunologic, and virologic status.

Ample precedent exists to provide a theoretical basis to justify evaluation of a polyclonal HIV immune globulin preparation for the prevention of perinatal HIV transmission. Administration of pooled antibody such as HIVIG from multiple donors provides a broad range of antibodies, which might neutralize maternal virus that endogenous maternal antibodies fail to neutralize. Antibodies present in such a polyclonal preparation might have activities in addition to neutralization, such as binding to NK cells to effect antibody-dependent cellular cytotoxicity, which while not neutralizing, could lyse infected cells and thereby prevent cell-to-cell transmission of virus. Administration of antibody may attenuate transmission by decreasing the amount of infectious virus in the maternal circulation, preventing HIV infection of placental cells, or providing protective antibody to the fetus during the last trimester of pregnancy and at delivery or by some combination of any or all of these mechanisms.

HIV is a major threat to child health. The only way to alter significantly the face of the AIDS epidemic in children is to prevent infection. The demonstration by ACTG protocol 076 that preventive pharmacotherapy can reduce transmission [21] provides assurance that development of such preventive strategies is feasible. As the AIDS epidemic matures and HIV mutates under the selective pressure of antiretroviral agents such as zidovudine, the need to develop and test other agents for this indication will become even more compelling.

Acknowledgments

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Study Group Members

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